## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 22 October 2007 has been entered.

### *Status of Application, Amendments and/or Claims*

The amendment of 13 August 2007 has been entered in full. Claims 11, 13, and 15 are amended. Claims 1-10, 12, 14, and 16-32 are cancelled.

Claims 11, 13, and 15 are under consideration in the instant application.

### *Withdrawn Objections and/or Rejections*

1. The objection to claim 11 at page 2 of the previous Office Action (24 April 2007) is *withdrawn* in view of the amended claim (13 August 2007).

2. The rejections to claims 11-13 and 15 under 35 U.S.C. 112, second paragraph, as set forth at pages 2-6 of the previous Office Action (24 April 2007) are *withdrawn* in view of cancelled claim 12 and amended claims 11, 13, 15 (13 August 2007).

3. The rejection of claims 11-13 and 15 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pages 11-13 of the previous Office Action (24 April 2007) is *withdrawn* in view of cancelled claim 12 and amended claims 11, 13, and 15 (13 August 2007).

4. The rejection of claims 11-13 and 15 under 35 U.S.C. § 112, first paragraph (new matter) as set forth at pages 13-14 of the previous Office Action (24 April 2007) is *withdrawn* in view of cancelled claim 12 and amended claims 11, 13, and 15 (13 August 2007).

5. The rejection of claims 11-13 and 15 under 35 U.S.C. § 102(b) as set forth at pages 14-15 of the previous Office Action (24 April 2007) is *withdrawn* in view of cancelled claim 12 and amended claims 11, 13, and 15 (13 August 2007).

***New Claim Rejections - 35 USC § 112, second paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 11, 13, and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claims 11, 13, and 15 are indefinite because it is not clear how an increased level of RELMβ in a tissue is properly determined. It seems that the claims are missing a comparison step with a baseline or a normal control (see for example, claim 11, line 7).

***Claim Rejections - 35 USC § 112, first paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 11, 13 and 15 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for determining if a patient has allergen-induced asthma comprising (a) measuring RELMβ mRNA expression in a biological sample isolated

from the patient, wherein the biological sample is lung fluid, lung biopsy, bronchoalveolar fluid, or combinations thereof and (b) comparing RELMβ mRNA to normal lung fluid, lung biopsy, bronchoalveolar fluid, or combinations thereof wherein an increased level of RELMβ mRNA as compared to normal indicates the patient has allergen-induced asthma, *does not reasonably provide enablement for* a physiological assessment method for determining if a patient has asthma, the method comprising determining a level of resistin-like molecule β (RELMβ) in a pulmonary tissue selected from the group consisting of lung fluid, lung biopsy, bronchoalveolar fluid, and combinations thereof, in the patient to assess whether the patient does or does not have asthma wherein an increased level of RELMβ in the tissue indicates the patient has asthma. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth at pages 6-11 of the previous Office Action of 24 April 2007 and at pages 4-8 of the Office Action of 14 November 2006.

Applicant's arguments (13 August 2007), as they pertain to the rejections have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At page 3 of the Response of 13 August 2007, Applicant argues that the specification qualitatively and functionally describes the effect of RELMβ on lung function (page 16, lines 6-21), lung histology (page 20, line 12 through page 22, line 21), and fibroblast motility (page 22, line 22 through page 23, line 21). Applicant asserts that this disclosure provides examples of how RELMβ levels can be determined by examining the physical effects of RELMβ on animal lung tissue or by evaluating it effect in an in vitro assay of fibroblast motility.

Applicant's arguments have been fully considered but are not found to be persuasive. Applicant is reminded that claim 11 is directed to "...determining a level of RELMβ in a pulmonary tissue..." (lines 2-3) [emphasis added by Examiner]. The examples cited by Applicant above measure lung function, lung histology, and fibroblast motility after the administration of RELMβ to mice or in *in vitro* assays. There is no guidance in the specification establishing the nexus between measurement of lung function, lung histology, and fibroblast motility as a level of RELMβ and a diagnosis of asthma. Furthermore, the assays in the specification provide little or no guidance as to how to measure RELMβ *qualitatively*. The Examiner acknowledges that the specification does provide an *in vitro* assay measuring effects of RELMβ on fibroblast motility. However, again, the Examiner is not clear how this *in vitro* assay (1) functionally determines RELMβ level in a patient's pulmonary tissue sample and (2) determines that the patient does/does not have asthma.

(ii) At page 3 of the Response, Applicant contends that protein expression is a readily determinable parameter, not requiring undue experimentation by one of ordinary skill in the art. Applicant indicates that RELMβ mRNA levels are increased in the rodent model of asthma inflammation (page 17, lines 16-31) and that the intratracheal application of RELMβ induces the hallmarks of pulmonary inflammation associated with asthma (page 20, line 12 through page 22, line 21). Applicant states that one skilled in the art can easily determine RELMβ protein levels in lung tissue by Western blot analysis and staining of tissue sections with the proper probe (page 28, line 2-7). Applicant points out the prior art cited by the Examiner (Artis et al.) discloses that changes in RELMβ protein expression can be readily detected by Western blot and

immunofluorescent stains of mouse tissue sections. Applicant concludes that undue experimentation is not required for one of ordinary skill in the art to determine increased RELMβ levels in lung tissue and fluids of patients.

Applicant's arguments have been fully considered but are not found to be persuasive. As discussed in the previous Office Action, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991). The present invention is unpredictable and complex wherein one skilled in the art may not necessarily assess if a patient has asthma by determining the level of RELMβ protein. Undue experimentation would required of one skilled in the art to determine RELMβ *protein* expression levels in the tissue of a patient, as required by claim 13. Although one skilled in the art can determine protein levels utilizing such assays as Western blot, the specification of the instant application has not provided a nexus between allergen-induced asthma and an increase in RELMβ *protein* level. Further experimentation is required by one skilled in the art to determine if such a nexus exists. Applicant's arguments are merely an invitation to the artisan to use the current invention as a starting point for further experimentation.

As mentioned in the Office Action of 14 November 2006 and reiterated herein below, the state of the art is such that protein expression levels are not predictable from the mRNA expression levels. For example, Lilley et al. teach that "DNA chips (mRNA profiling studies)

can contribute to the study of gene expression in response to a particular biological perturbation. However, the extrapolation that changes in transcript level will also result in corresponding changes in protein amount or activity cannot always be made" ("Proteomics" Molecular Biology in Cellular Pathology, (2003) England: John Wiley & Sons, page 351). King et al. disclose that "it has been established that mRNA levels do not necessarily correlate with protein levels" (pg 2287, 2nd full paragraph). King et al. state that it has been demonstrated that correlation between mRNA and protein abundance is less than 0.5 and that "mRNA expression studies should be accompanied by analyses at the protein level" (pg 2287, bottom of col 1 through the top of col 2). Haynes et al. teach that "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks).

(iii) The specification of the instant application teaches that the level of mRNA for RELMβ is evaluated in lung from mice challenged with different allergens in different models of allergen-induced asthma (pg 7, lines 10-24 through pg 10; pg 17). The specification discloses that expression of RELMβ mRNA is significantly increased during allergen induced asthma compared to control mice (pg 16, lines 22-24; pg 17, lines 10-24 through pg 18; Figures 1-2). The specification also teaches that allergic lung inflammation is associated with marked and specific ectopic expression of RELMβ in the lung, which is in contrast to prior work (pg 26, lines 8-12). The state of the art is such that various irritants trigger asthma, such as allergens (pollen, animal dander, mold), dust mites, smoke, air pollutants, cold air, medications, physical exertion,

and strong odors, among others (see Appendix A attached to the instant Office Action). However, the instant specification does not teach increased RELMβ mRNA or protein levels in any other asthma, besides allergen-induced asthma. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed". In this case, Applicant's single example in the specification of measuring an increased level of mRNA for RELMβ in mice with allergen-induced asthma is not adequate guidance, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. The skilled artisan must resort to trial and error experimentation to determine if asthma resulting from other irritants is also associated with an increased level of RELMβ. Such trial and error experimentation is considered undue.

***Conclusion***

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on (571) 272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
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